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Shooting the messenger: Targeting signal transduction pathways in leukemia and related disorders

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Abstract

Traditional treatments for leukemia and myeloproliferative disorders have involved invasive clinical regimes, including chemotherapy, phlebotomy, and bone marrow transplantation, together with supportive care. These have been of variable effectiveness and have often elicited

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adverse, sometimes life-threatening side effects. Perturbation of key signal transduction pathways has become a consistent finding in the pathophysiology of leukemia and related diseases. This has allowed the development of specific pharmacological agents targeting deviant pathway component(s). Of this class of therapeutics those directed at the leukemic oncoproteins BCR-ABL and PML-RARα have provided proof-of-concept of the approach and are now established mainstream therapies. Specific inhibitors for the JAK2 tyrosine kinase are now in active development for myeloproliferative disorders and may become a new class of targeted therapeutics. However, an emerging motif in the field is the convergence of multiple mutant pathways on key downstream messengers, such as STAT5 or PI3-kinase, which therefore constitute potential new therapeutic targets.

Keywords: Leukemia; Myeloproliferative disorders; Signaling pathways; Therapeutics; BCR-ABL; JAK2; STAT5; PI 3-kinase; HDAC

1. Introduction

Hematopoiesis is an intricate process in which a limited pool of stem cells both self renew and generate multi-lineage progenitor cells that then produce lineage-restricted precursors from which all mature hematopoietic cell populations are generated. This process is highly regulated by a complex network of signaling molecules. Perturbation of these signals can lead to the uncontrolled expansion of one or more of these cell populations, leading to a variety of hematopoietic diseases. Principal amongst these are those classified as leukemias and myeloproliferative disorders (MPDs), each of which is actually a spectrum of disorders with variable etiology and clinical course [1–3].

Leukemias pose a significant health burden, with an estimated 44,790 new adult cases being diagnosed in the United States of America in 2009 [4], while MPDs account for a significant burden of disease in an older cohort of patients. Advances in both basic and clinical science have seen increased understanding of both leukemias and MPDs at the molecular level in recent years [5,6]. These insights have led to the development of specific pharmaceuticals to treat these diseases, with the real possibility of tailoring therapies to specific patients depending on their individual disease molecular profile [7,8]. However, with so many molecular changes now known to contribute to these diseases, and the increasing incidence of resistance to these drugs, more specific therapies are required. These include second-generation compounds that overcome resistance and other clinical problems, as well as entirely new therapeutic strategies [9–11].

1.1. Leukemia

The term leukemia ('white blood') came from post mortem examinations of the blood from afflicted patients, and reflects the high white blood cell counts experienced by most leukemia patients prior to treatment [12]. Frequently, these extra white blood cells are immature or dysfunctional. Leukemias interfere with normal bone marrow function resulting in reduced numbers of red blood cells, platelets, and leukocytes, leading to anemia, defective blood clotting, infection and immune suppression [13].

Leukemias are classified depending on the clinical tempo of disease progression, the lineage of the malignant population, and the degree of differentiation. The most common forms are acute myeloid leukemia (AML), with eight subtypes (M0-7), acute lymphoblastic leukemia (ALL), with three sub-types (L1-3), and chronic lymphocytic leukemia (CLL) [14]. Chronic myelogenous leukemia is considered under myeloproliferative disorders below.

1.2. Myeloproliferative disorders

The MPDs are a group of clonal diseases of the bone marrow in which excess myeloid cells are produced, including red blood cells, platelets, and various myelomonocytic lineage cells. On the whole MPDs have a much better prognosis than acute leukemias. The four most common MPD variants are chronic myelogenous leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET) and idiopathic myelofibrolysis (IMF), but the spectrum of disorders also includes chronic eosinophilic leukemia (CEL), chronic neutrophilic leukemia (CNL), systemic mastocytosis (SM) and basophilic leukemia [12,14]. These are probably best viewed as a continuum, rather than as distinct entities [15,16].

2. Traditional therapies

Traditional treatment strategies for leukemia include stand-alone chemotherapy, or chemotherapy in combination with radiation therapy or stem cell transplantation [17–19]. The standard chemotherapy regimen either kills malignant cells to achieve remission, or damages them to slow the progress of the disease. Although directed toward certain macromolecules or enzymes, conventional chemotherapy typically does not discriminate effectively between rapidly dividing normal cells (such as the gastrointestinal tract) and the malignant population, hence resulting in toxic side effects. In general, combinations of drugs are used for the initial, induction phase of chemotherapy. Such combination chemotherapy usually offers the benefits of early remission and a lower risk of disease resistance. Consolidation and maintenance treatments are intended to prevent disease recurrence. Consolidation treatment often entails a repetition of induction chemotherapy or the intensifica-